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Synthesis and Biological Activity of Lactones *en route* to Altohyrtin A

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Abstract: Lactones **2** and **7** were synthesised and tested against six human tumour cell lines (*Pancreas-a*, BXPC-3), (*Thyroid ca*, KAT-4), (*Thyroid ca*, SW1736), (*Lung*-NSC, NCI-H460), (*Pharynx*-sq, FADU) and (*Prostate*, DU-145). Lactone **7** proved inactive, but lactone **2** displayed some activity against four of the six cell lines examined. Both lactones were converted into an intermediate **5** *en route* to Altohyrtin A.

We have previously reported[1] some of our synthetic approaches to the cytotoxic marine macrolide Altohyrtin A[2,3] (Figure 1). Herein we report the elaboration of ene-ester **1**[1] and diol **6**[1] to the lactone aldehyde **5**, confirming the stereochemical integrity of our synthetic route and providing key building blocks for the C-37 to C-43 perimeter in our synthesis. The lactones **2** and **7** were evaluated for their biological activity against six human tumour cell lines.[4]

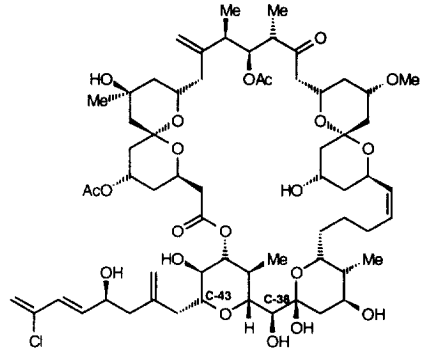

Figure 1

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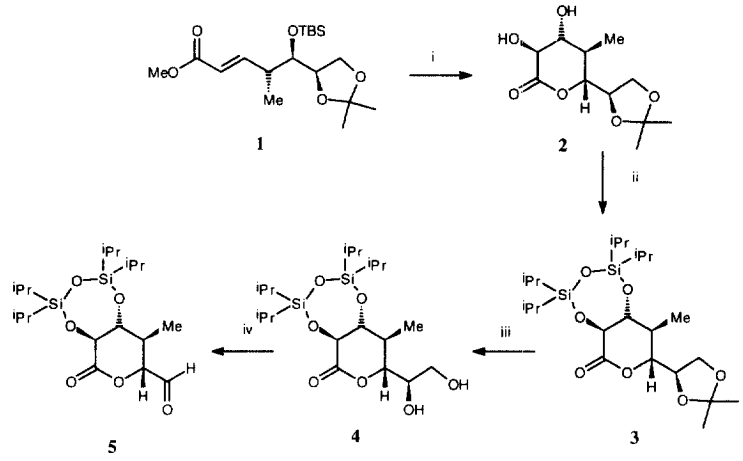
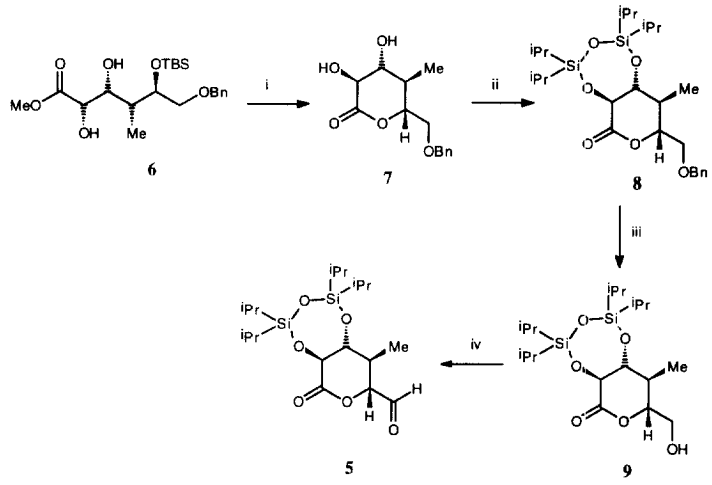
Ene ester **1** was subjected to a Sharpless type *bis*-hydroxylation using a 'Super AD-mix β' formulation[1] and the intermediate diol was purified by flash column chromatography prior to desilylation. Under the TBAF deprotection conditions spontaneous cyclisation furnished the lactone diol **2** in a 50% overall yield from the ene-ester **1**. It was necessary to leave the diol unprotected for successful cyclisation, since treatment of the *bis*-acetonide or *bis*-MOM derivative of **2** with TBAF in THF led to decomposition.



Reagents and Conditions : i)a) Super AD-mix β formulation, $MeSO_2NH_2$, $^tBuOH/H_2O$ (1:1), b)TBAF, THF, (50% over 2 steps); ii) $(^iPr_2SiCl)_2O$, DMF, imidazole, (100%); iii)TFA/$CHCl_3$ (1:8); iv) $NaIO_4$, H_2O/THF (1:20), (73% over 2 steps).

Scheme 1

Elaboration of the lactone diol **2** to the bridged silyloxy compound **3** was achieved in quantitative yield by treatment with $(^iPr_2SiCl)_2O$ and imidazole in DMF. Chemoselective removal of the isopropylidene group of **3** was achieved by brief treatment with TFA in $CHCl_3$.[5] Oxidative cleavage of the diol **4** using $NaIO_4$ in aqueous THF gave the lactone aldehyde **5** in a respectable yield of 73% over the two steps. An alternative strategy for the synthesis of the lactone aldehyde **5** is described in Scheme 2.



Reagents and Conditions : i)TBAF, THF, (65%); ii) ($^{i}Pr_2SiCl)_2O$, DMF, Im, (76%); iii)H_2, Pd/C, EtOAc, (19%); iv) Swern Oxidation (70%).

Scheme 2

The known diol **6**[1] was treated with TBAF in THF to generate the triol which spontaneously lactonised under the reaction conditions to give the lactone diol **7**. This diol **7** was protected as the bridged siloxy adduct **8**. Debenzylation furnished the primary alcohol **9** in a disappointing yield. The alcohol **9** was oxidised using the Swern protocol[6] to give the lactone aldehyde **5**.[7] The two lactone diol intermediates **2** and **7** were tested for biological activity against six human tumour cell lines.[4] In each case, the GI_{50}, TGI and LC_{50} were measured. A value of <10 μg / ml is considered to be active.

Cell Type	Cell Line	GI_{50}/(μg/ml)	TGI/(μg/ml)	LC_{50}/(μg/ml)
Pancreas-a	BXPC-3	>10	>10	>10
Thyroid ca	KAT-4	>10	>10	>10
Thyroid ca	SW1736	8.5	>10	>10
Lung-NSC	NCI-H460	2.9	>10	>10
Pharynx-sq	FADU	3.7	>10	>10
Prostate	DU-145	2.7	>10	>10

Table - Biological data for lactone **2**

Compound **7** showed no biological activity, whereas compound **2** displayed a marginal activity against thyroid, lung, pharynx and prostate cancer cell lines (Table). Although the Altohyrtin family of compounds typically show values in the 10^{-5} μg / ml range the noteworthy activity of compound **7** may provide a lead into the development of simpler, more accessible, analogues of Altohyrtin that are amenable to commercial development.

Acknowledgements

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References

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4. We thank Professor G.R. Pettit for communication of these results from his laboratory at the Arizona State University.
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6. Swern, D., Omura, K., *Tetrahedron*, 1978, 34, 1651.
7. Physical characteristics of compound **5** - R_f (EtOAc) 0.67; (Found: M^++H, 417.21353. $C_{19}H_{37}O_6Si_2$ requires *M+H*, 417.21287); $[\alpha]_D^{22}$ +4.7 (*c* 2.33, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3020, 2948 and 2869 (sp^3 CH_3), 1746s (C=O); δ_H (300 MHz; $CDCl_3$) 0.96-1.13 (28H, m, 4 x ^{i}Pr), 1.20 (3H, d, *J*=6.6Hz, MeCH), 2.07-2.18 (1H, m, MeCH), 3.80 (1H, dd, *J*=9.0Hz and 9.6Hz, O=CCH(O)CH(O)), 4.19 (1H, d, *J*=8.7Hz, O=CCH(O)), 4.23 (1H, dd, *J*=2.1Hz and 10.5Hz, MeCH(O)CHCHO), 9.60 (1H, d, *J*=2.1Hz, CHO); δ_C (75 MHz; $CDCl_3$) 11.22, 11.56, 11.91, 12.09 and 13.19 (CH of 4 x ^{i}Pr and MeCH), 16.08, 16.17, 16.23 and 16.33 (CH_3 of ^{i}Pr), 35.43 (MeCH), 75.50 and 76.36 (2 x CH(OSi)), 82.65 (CH(O)CHO), 167.19 (lactone C=O), 194.89 (aldehyde C=O); *m/z* (CI) 434 (M^++NH_4, 100%), 417 (M^++H, 15%).